REMARKS

No amendments to the claims are made herein although a listing of the claims is provided for the Examiner's convenience. Claims 21-38, 40, 75, and 76 are currently pending.

I RESPONSE TO THE REJECTION OF CLAIMS 1-38, 40, AND 75-76 UNDER 35 U.S.C. § 103(a)

Claims 1-38, 40, 75 and 76 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Davenport *et al.*, August 16, 1996, Pediatric Pulmonology, S13, Abstract 34, ("Davenport") taken with Ubillas *et al.*, 1994, Phytomedicine 1:77-106, ("Ubillas"), U.S. Patent No. 4,698,360 to Masquelier ("Masquelier"), U.S. Patent No. 5,043,160 to Wursch ("Wursch"), Remington's Pharmaceutical Sciences ("Remington's") and Applicants' admissions.

The Examiner contends that Davenport teaches the oral administration of SP-303, an aqueous soluble proanthocyanidin polymer composition isolated from *Croton* species, to treat secretory diarrhea in an animal; and that the mechanism of action of the compound involves inhibition of cAMP-mediated chloride secretion. The examiner further alleges that it would have been obvious to modify the invention of Davenport and Ubillas by providing compositions of aqueous soluble proanthocyanidins for oral ingestion which are formulated to protect the proanthocyanidins from the stomach environment and that inhibit or neutralize stomach acid or which are slow release formulations according to the teachings of Masquelier, Wursch and Remington's. The Examiner contends that the references clearly teach that the technology is well known in the art and that it would have been obvious to provide compositions for treating secretory diarrhea by inhibiting fluid accumulation and cAMP-mediated chloride secretion as demonstrated by Davenport.

Applicants respectfully but emphatically disagree. As set forth below, nothing in the cited combination of references suggests the presently claimed methods.

Applicants remind the Examiner that she had previously rejected the claims under 35 U.S.C. § 103(a) based upon Ubillas, Masquelier, Wursch, Remington's and Applicants' admissions in the office action dated January 8, 2004. The Examiner had alleged that it would have been obvious to modify the method of treating diarrhea taught by Ubillas to formulate the proanthocyanidins to protect them from the stomach environment, based

upon the teachings of Masquelier, Wursch and Remington's. Briefly, in a Response dated July 6, 2004, Applicants argued that Ubillas does not disclose administration of an isolated proanthocyanidin formulation and teaches away from the need to enterically protect the proanthocyanidins. In addition, the secondary references also teach away from enteric protection of proanthocyanidin polymer compositions and/or relate to compounds which are structurally unrelated to the claimed proanthocyanidins. Applicants also provided a Declaration of Dr. Akram Sabouni with the July 6, 2004 response, which provides evidence that the claimed, isolated proanthocyanidin polymer composition is labile in the stomach environment and attesting that, when the inventors made this discovery, this result was surprising to him and his colleagues working in the field. Accordingly, Applicants argued that absent impermissible hindsight reconstruction based upon the present disclosure, there would have been no motivation to combine Ubillas with the secondary references and thus, the references do not render the claims obvious.

The Examiner acknowledged that Applicants had overcome this rejection in the Office Action dated September 17, 2004.

In response to the current rejection, Applicants respectfully submit that Davenport does not cure the defect in the rejection previously made in the January 8, 2004 Office Action and admittedly overcome by Applicants arguments. There is no suggestion, much less any teaching in Davenport for the isolated, proanthocyanidin polymer from Croton to be enterically protected in order to be useful for use as an anti-diarrheal agent. Davenport reports the administration by gavage of SP-303 (an isolated proanthocyanidin polymer composition isolated from a Croton species) in $NaHCO_3$ as a delivery vehicle in an animal model of secretory diarrhea, using $NaHCO_3$ alone as a negative control in the reported experiment. The abstract reports that "SP-303, administered by gavage, significantly inhibited fluid accumulation ...whereas ...administration of $NaHCO_3$ alone did not." Davenport further states that "SP-303 may be a effective inhibitor of cAMP-mediated Cl^- secretion and may be acting directly on the CFTR Cl^- channel." Davenport et al. abstract.

Davenport's disclosure of administering proanthocyanidin in $NaHCO_3$, relative to $NaHCO_3$ alone, to inhibit fluid accumulation in the cholera toxin-induced model of secretory diarrhea, does not render the herein claimed subject matter obvious. Davenport does not suggest to a person of ordinary skill that the isolated proanthocyanidin polymer composition must be formulated to protect the proanthocyanidin polymer composition from

the stomach environment. While Davenport happened to use the buffer $NaHCO_3$ to formulate the SP-303 for administration by gavage, Davenport does not teach or suggest what the inventors of the instant application discovered, *viz.*, to be effective for treatment of diarrhea, the proanthocyanidin formulation must somehow be protected from the acid environment of the stomach. Thus, Davenport does not suggest formulating the claimed proanthocyanidin polymer composition to protect it from the stomach environment as a controlled release preparation or to coat the composition with an enteric coating and, thus, does not render the invention obvious.

None of Ubillas, Masquelier, Wursch, Remington's or applicants' admissions, either alone or in combination, cure the defect of Davenport. All of these references have been discussed in detail in prior responses, such as the July 6, 2004 response, but these references are treated again briefly below. With respect to Ubillas, while Ubillas discloses that the *Croton lechleri* sap can be administered in milk, Ubillas also discloses that the *Croton lechleri* sap can be administered in water or alcohol (Ubillas at page 78, second column), neither of which protect against the stomach environment. Further, Ubillas provides no suggestion for formulating the isolated proanthocyanidin polymer composition to specifically protect it from the stomach environment. In fact, teaching that the sap can be effectively administered in water or alcohol teaches away from the present invention since, from Ubillas, one skilled in the art would believe that proanthocyanidin polymer compositions could be administered effectively without any sort of enteric protection. Thus, rather than making the claimed invention obvious, Ubillas actually teaches away from the claimed invention.

Masquelier specifically teaches sugar coated pills for oral administration (Masquelier col. 6, lines 26-28). Sugar coating readily dissolves in an aqueous environment regardless of the pH and, thus, would not be effective to protect the proanthocyanidin from the stomach environment. In fact, Masquelier does not suggest the oral administration of dried proanthocyanidin extract in an enteric coating for any purpose nor does Masquelier teach or even suggest that enteric protection is necessary or preferred for oral administration of the proanthocyanidin. Masquelier teaches administration of the proanthocyanidin extract in various vehicles for oral administration that do not protect against stomach acid (Masquelier at col. 6, lines 26-28). Thus, Masquelier does not suggest to the ordinarily skilled artisan that the proanthocyanidin extract should be formulated in an enteric coating, and, in fact, teaches away from the need for such a formulation.

Wursch relates to water insoluble tannins extracted from carob pods while the present invention is directed to water soluble proanthocyanidin polymers from *Croton* and *Calophyllum* species. Thus, the composition in Wursch is completely different and formulations of the Wursch composition have no bearing on the present formulations. In short, there is no combination to combine Wursch with Davenport because each teaches the use of very different compounds. Assuming, *arguendo*, that Wursch is even relevant, the formulations taught by Wursch are not aimed to protect the tannin composition but to sugar-coat the composition so young children will ingest it. Unlike the teachings of the present specification, Wursch does not suggest the oral administration of any proanthocyanidin composition in an enteric coating, and does not teach the administration of tannins in any formulation in order to protect the tannins from the stomach environment.

Remington's is a compendium of pharmaceutical formulations and teaches a very large number of formulations, including enterically protected formulations as well as many, many more formulations that are not enterically protected. Without specific teachings or suggestion to pick that one formulation out of a substantial laundry list of formulations, there is no motivation to specifically choose any specific formulation for the composition, and therefore, Remington's in combination with any of the references does not render the claimed formulations obvious.

The Examiner also relies upon Applicants' statements that methods for making enteric formulations are well known in the art. However, these statements are merely cumulative to the disclosure of Remington's and do not in any way make up for the deficiencies in the cited references.

In sum, Davenport does not teach or suggest the claimed formulations of the isolated proanthocyanidin polymer and the secondary references either teach away from enteric protection of the polymer or are not relevant to formulations of the claimed proanthocyanidin polymer composition. Accordingly, the cited references, even in combination, do not render the pending claims obvious. Applicants respectfully request that the rejection be withdrawn.

IV CONCLUSION

Applicants believe that they have addressed all the issues outstanding in connection with the present application. Accordingly, reconsideration and an early allowance

of the present application in view of the above remarks is respectfully requested. Applicants respectfully request that the Examiner call the undersigned if any questions or issues remain.

Respectfully submitted,

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